COMPUTATIONAL APPROACHES TO DRUG DESIGN AND OVERCOMING DRUG RESISTANCE.

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The concept of protein structure-based drug design has been exploited to develop novel structural classes of inhibitors for several target enzymes (1). Where a particular functional group in an inhibitor's structure is associated with the development of resistance, this approach can be used to re-engineer a potent inhibitor that does not contain the functional group responsible for resistance. For classical antifolate drugs, which contain a glutamate residue, drug resistance often develops by two mechanisms related to the glutamate function: deletion of active transport, or decreased activity of folylpolyglutamate synthetase (FPGS). In both cases, the drug resistance can be circumvented by designing lipophilic antifolates. The use of protein structure-based design approaches will be discussed in connection with the folate cofactor-requiring enzyme thymidylate synthase (TS), whose 3-dimensional structure has been determined to high resolution by X-ray crystallography (2). Computational techniques used in the design process included GRID, 3-D data base searches, and Monte Carlo-based *de novo* ligand design tools (3, 4). As expected, the resulting inhibitors retained full activity against tumor cells with membrane transport defects or with altered FPGS.

Computational approaches have also been employed at the level of biochemical pathways, intact cells, or the whole animal, to address a variety of questions involving drug resistance. Our approach combines kinetic simulation of metabolic pathways with cytokinetic modelling and pharmacokinetic modelling (5). Three situations involving resistance to HIV will be discussed: (a) How effective is the "convergent blockade" strategy (in which multiple inhibitors are directed at a common target enzyme) likely to be? (b) What are the possible causes for failure of early AZT therapy in the "Concorde" study? This study appeared to contradict the general rule that drug resistance is less probable when the pathogen burden is small. (c) How can we optimize use of cellular antimetabolites (e.g. hydroxyurea) to potentiate AZT, and does this strategy delay the onset of resistance? The ability to simulate drug effects on complex biological systems facilitates the design and analysis of novel strategies to minimize or delay failure of chemotherapy resulting from acquired drug resistance.

REFERENCES

1. K. Appelt et al., J.Med.Chem. 34: 1925-1934 (1991).
2. D.A. Matthews et al., J.Mol.Biol. 214: 923-936 (1990).
3. M.D. Varney et al., J.Med.Chem. 35: 663-676 (1992).
4. S.E. Webber et al., 36: 733-746 (1993).
5. R.C. Jackson, "The Theoretical Foundations of Cancer Chemotherapy", 447 pp. San Diego, Academic Press (1992).